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Uric Acid: the Past Decade

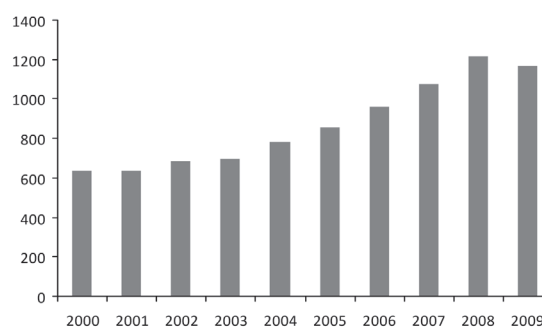
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In the greater tree of life, the "rise" of uric acid in the circulation of living organisms is a relatively recent event (1). In the majority of species that generate uric acid as the end product of purine metabolism, urate is transformed into a more soluble allantoin by urate oxidase ("uricase") (2). However, it is presently believed that some 10-20 million years ago 2 independent mutations in the uricase gene occurred and were kept in a very small subset of species (including the ancestors of apes and humans) – most likely by positive selection (3). Many elements of this story remain a mystery even to this date. Why did some primates lose uricase activity some 15 million years ago? What was the selective advantage of having 10-fold higher serum urate levels compared with other mammals? Was it related to the development of cognitive abilities? Did it serve as a protection against infectious agents of those times? Did it buffer the effects of oxidative stress and contribute to present-day longevity? Why do male humans have much higher serum levels than female? Is uric acid a friend or a foe – is it a protective factor or a risk factor, and against (or for) what? What levels should be considered too high? Or too low? What causes the variation in its levels within and between humans? All these fundamental questions remain unanswered to this day (4,5).

Partially because of these long-standing mysteries, the interest in uric acid among the researchers is steadily increasing. This is reflected in a growing number of articles related to this topic over the past decade. After studying several recent references that compared different search tools, we established that Web of Science's search tools were most appropriate to our needs (6-8). We conducted a search of the *Web of Science* (9) using search terms: "uric acid" OR "urate" OR "hyperuric(a)emia" OR "hypouric(a)emia." The search was performed for all fields for the period between 1 January, 2000 and 30 December, 2009 and it returned 8715 articles. The distribution of those articles by year of publication is shown in Figure 1. The number of

publications related to this topic has doubled over the period of interest, from just above 600 in each year to more than 1200 in 2008. The "decrease" in 2009 is most likely an artifact, because there are still unprocessed articles from 2009 that will eventually appear on the Web of Science in early 2010. The 8715 articles have been cited 88 508 times, which gives an average citation per item of 10.2 times. However, this indicator is not very useful because the period of citation ranged from 9 years (for articles published in 2000) to 0 years (for articles published in 2009). Assuming that all the articles had a median period during which they could have accumulated citations anywhere between 3-4 years (given that the majority was published in the second part of the decade), this gives "citation intensity" for an average article of about 3 citations in each year, which is also indicative of the level of activity in this field.

Figure 1.



The distribution of 8715 articles on the *Web of Science* (4) that contained key words "uric acid," "urate," "hyperuric(a)emia," or "hypouric(a)emia" by the year of publication within the past decade.

Table 1 shows countries, institutions, and journals of origin of the articles related to uric acid, urate, hyper- or hypouric(a)emia published between 2000 and 2009 and indexed by the Web of Science. Most of the ar-

TABLE 1. Countries, institutions, and journals of origin of the articles related to uric acid, urate, hyper- or hypouricemia between 2000 and 2009

Rank	Publication source	No.	%
Country			
1	United States of America	2194	25.18
2	Japan	907	10.41
3	PR China	626	7.18
4	Italy	483	5.54
5	Germany	475	5.45
6	England	473	5.43
7	Spain	442	5.07
8	Taiwan	349	4.00
9	Turkey	339	3.89
10	India	323	3.71
Institution			
1	University of Florida	134	1.54
2	Harvard University	113	1.30
3	University of Texas	91	1.04
4	University Ioannina	80	0.92
5	University of Pennsylvania	72	0.83
6	Baylor College of Medicine	65	0.75
7	University of Tokyo	62	0.71
8	University of Minnesota	61	0.70
8	University of Pittsburgh	61	0.70
10	University of Alabama	57	0.65
Journal			
1	<i>Journal of Hypertension</i>	143	1.64
2	<i>Electroanalysis</i>	125	1.43
3	<i>Arthritis and Rheumatism</i>	108	1.24
4	<i>Journal of Rheumatology</i>	94	1.08
5	<i>Kidney International</i>	89	1.02
6	<i>Nephrology Dialysis Transplantation</i>	84	0.96
7	<i>Free Radical Biology and Medicine</i>	82	0.94
7	<i>Journal of the American Society of Nephrology</i>	82	0.94
9	<i>Biosensors & Bioelectronics</i>	74	0.85
10	<i>Annals of the Rheumatic Diseases</i>	66	0.76

ticles came from the USA (25%), followed by Japan (10%), China (7%), Italy (6%), Germany (5%), England (5%), and Spain (5%). Two somewhat surprising entries into top 10 are Taiwan and Turkey, which may be explained by a high prevalence of hyperuricemia and gout in these countries (10,11). Among the institutions, most of the articles were generated by the groups from the University of Florida, followed by their colleagues from Harvard University. The list is dominated by US institutions, with University of Tokyo, in the 7th place, being the only non-US institution among the top 10. *Journal of Hypertension* leads the list of journals that were most receptive to publishing

the research related to uric acid, with more than 14 articles published on this topic in each year. It is followed by *Electroanalysis*, a couple of rheumatology journals, and two nephrology journals. This list reflects our current understanding of the role of uric acid in affecting blood pressure, gout, kidney disease, as well as its potential anti-oxidant properties. To underscore the importance of the latter, the journal *Free Radicals Biology and Medicine* is also on the list, in the 7th place.

After this initial analysis of the number and distribution of the articles published during the last decade on the topic of uric acid, we tried to identify the 10 articles (among 8715) which represented the most significant breakthroughs over the past decade. We were particularly interested whether there were truly novel insights providing some answers to the set of fundamental questions that was outlined in the introduction of this article. We used the Web of Science to investigate the number of citations received by each of the 8715 articles over a decade. To ensure fairness to all the articles included in the analysis, which had different time periods following their publication to pick up citations, we did not rank them by the total number of citations received but rather by "citation intensity." We defined "citation intensity" as the average number of citations received by each article in each year following the publication. This indicator should be more stable and should still recognize the achievements that generated the most interest among the other researchers, even for the articles that have been published relatively recently. Only the most recently published articles (eg, those published in the past year) were slightly disadvantaged by this approach. Furthermore, we only considered articles that were clearly focused on uric acid, rather than those that were returned because of indirect interest in uric acid, which was not clear from the title and/or abstract. The 10 most significant insights during the past decade according to this indicator are shown in Table 2.

The clear "winner", ie, the most significant research progress over the past decade related to uric acid, was the article by Martinon et al published in *Nature* in 2006. The authors discovered a molecular mechanism by which the deposition of monosodium urate (MSU) or calcium pyrophosphate dihydrate (CPPD) crystals in hyperuricaemic patients induce inflammation in gout and pseudogout disease. They showed that MSU and CPPD engaged the caspase-1-activating NALP3 (also called cryopyrin) inflammasome. This results in the production of active interleukin (IL)-1 beta and IL-18. They proved their hypothesis by demonstrating that macrophages from mice deficient in various components of the

TABLE 2. The 10 articles with the greatest “citation intensity” (average number of citations received per each year following the publication) among 8715 articles indexed by the Web of Science on the topic of uric acid, urate, and hyper- and hypouric(a)emia

Rank	Authors	Title	Journal	Year	Volume	Pages	Cumulative Citations	per year
1	Martinon F, Petrilli V, Mayor A, et al.	Gout-associated uric acid crystals activate the NALP3 inflammasome	<i>Nature</i>	2006	440	237-241	402	100.50
2	Kool M, Soullie T, van Nimwegen M, et al.	Alum adjuvant boosts adaptive immunity by inducing uric acid and activating inflammatory dendritic cells	<i>Journal of Experimental Medicine</i>	2008	205	869-882	85	42.50
3	Johnson RJ, Kang DH, Feig D, et al.	Is there a pathogenetic role for uric acid in hypertension and cardiovascular and renal disease?	<i>Hypertension</i>	2003	41	1183-1190	243	34.71
4	Fang J, Alderman MH	Serum uric acid and cardiovascular mortality - The NHANES I epidemiologic follow-up study, 1971-1992	<i>JAMA</i>	2000	283	2404-2410	333	33.30
5	Enomoto A, Kimura H, Chairoungdua A, et al.	Molecular identification of a renal urate-anion exchanger that regulates blood urate levels	<i>Nature</i>	2002	417	447-452	264	33.00
6	Vitart V, Rudan I, Hayward C, et al.	SLC2A9 is a newly identified urate transporter influencing serum urate concentration, urate excretion and gout	<i>Nature Genetics</i>	2008	40	437-442	56	28.00
7	Nakagawa T, Hu HB, Zharikov S, et al.	A causal role for uric acid in fructose-induced metabolic syndrome	<i>American Journal of Physiology - Renal Physiology</i>	2006	290	F625-F631	105	26.25
8	Khosla UM, Zharikov S, Finch JL, et al.	Hyperuricemia induces endothelial dysfunction	<i>Kidney International</i>	2005	67	1739-1742	122	24.40
9	Becker MA, Schumacher HR, Wortmann RL, et al.	Febuxostat compared with allopurinol in patients with hyperuricemia and gout	<i>New England Journal of Medicine</i>	2005	353	2450-2461	118	23.60
10	Mazzali M, Hughes J, Kim YG, et al.	Elevated uric acid increases blood pressure in the rat by a novel crystal-independent mechanism	<i>Hypertension</i>	2001	38	1101-1106	204	22.67

inflammasome (such as caspase-1, ASC, and NALP3) were defective in crystal-induced IL-1 beta activation (12). This article was cited about 100 times in each year after its publication, in comparison with an average of 3 in this field (9).

In the second place, there is an unexpected insight published by Kool et al in the *Journal of Experimental Medicine* in 2008. The authors realized that the mechanism by which alum adjuvant boosts adaptive immunity is the induction of uric acid and activation of inflammatory dendritic cells. Alum (aluminum hydroxide) is the most widely used adjuvant in human vaccines, but the mechanism of its adjuvanticity had been unknown. The authors showed that inflammatory dendritic cells-driven responses were abolished in MyD88-deficient mice and after uricase treatment, suggesting that alum adjuvant is immunogenic by exploiting “nature’s adjuvant,” the inflammatory dendritic cells, through induction of the endogenous danger signal – uric acid (13). This is a potentially very significant discovery that may partially explain why there was a positive selection on uricase mutations in some primates over the past 15 million years.

The third and fourth place are held by two epidemiological studies led by Johnson (14) and Fang (15) and published in *Hypertension* and *JAMA*, respectively. The studies used longitudinal design and large sample sizes to clarify the role of urate levels in hypertension and cardiovascular and renal disease – ie, some of the most common human diseases and conditions responsible for a considerable portion of global disease burden, both in terms of morbidity and mortality. The studies suggested that increased serum uric acid levels were independently and significantly associated with risk of cardiovascular mortality and the development of hypertension, vascular disease, and renal disease. Still, the authors agreed that further research would be needed to establish whether the nature of these apparent associations was causal and what the exact molecular mechanisms were (14,15).

The fifth and sixth most significant articles according to citation intensity were both focused on understanding of the renal urate reabsorption system, which maintains high concentration of uric acid in human se-

rum. It was known that 70% of daily urate disposal occurs via the kidneys, and that in 5%-25% of the human population hyperuricemia develops because of impaired renal excretion. It was also known that about 10% of people with hyperuricemia progress to develop gout, an inflammatory arthritis that results from deposition of monosodium urate crystals in the joint. However, the molecular basis for urate handling in the human kidney was unclear because of difficulties in understanding diverse urate transport systems and species differences (16). The first important insight was published by Enomoto et al in *Nature* in 2002. They identified what they thought was the long-hypothesized urate transporter in the human kidney and called it URAT1 (encoded by the gene SLC22A12). It was indeed a urate-anion exchanger regulating blood urate levels. The authors also showed that patients with idiopathic renal hypouricemia had defects in SLC22A12 (16). However, in the second part of the decade one of the first genome-wide association studies (published by Vitart et al in *Nature Genetics* in 2008) identified genetic variants within another transporter gene, SLC2A9, that explained much more of the variance in serum uric acid concentrations than URAT1. Common genetic variants in SLC2A9 were also associated with low fractional excretion of uric acid and with gout disease. The activity of SLC2A9 in uric acid transport was several times greater than that of the URAT1, as shown by functional experiments in *Xenopus laevis* oocytes. This finding was entirely surprising because SLC2A9 was a known fructose transporter. The power provided by genome-wide association strategies and supporting high-throughput genomic and bioinformatic technologies was critical in revealing its importance in uric acid transport (17).

The seventh on the list is the article by Nakagawa et al published in *American Journal of Physiology – Renal Physiology* in 2006. The authors established a causal role for uric acid in fructose-induced metabolic syndrome. They proposed that a marked increase in total fructose intake (in the form of table sugar and high-fructose corn syrup) in the recent decades may have substantially contributed to the epidemic of metabolic syndrome. They proposed that fructose raised uric acid, which in turn inhibited nitric oxide bioavailability. However, insulin requires nitric oxide to stimulate glucose uptake. Thus, fructose-induced hyperuricemia may have a pathogenic role in metabolic syndrome. A series of related experiments conducted in rats provided the first evidence that uric acid may be a cause of metabolic syndrome, possibly due to its ability to inhibit endothelial function (18).

The eighth article on the list, published by Khosla et al in *Kidney International* in 2005, was focused on the possible effects of hyperuricemia on the induction of endothelial dysfunction. The underlying hypothesis was that hyperuricemia generated reactive oxygen species and subsequent endothelial dysfunction through effects on xanthine oxidase activity, and that inhibition of xanthine oxidase with allopurinol can reverse endothelial dysfunction. The authors further hypothesized that uric acid induced endothelial dysfunction by inhibiting nitric oxide production. In a series of well-designed experiments in rats they showed that hyperuricemic rats had a decrease in serum nitric oxide, which is reversed by lowering uric acid levels with allopurinol, and that soluble uric acid also impaired nitric oxide generation in cultured endothelial cells thus inducing endothelial dysfunction (19).

The ninth article in the top 10 was written by Becker et al and published in the *New England Journal of Medicine* in 2005. It compared the new drug Febuxostat with allopurinol in patients with hyperuricemia and gout. Febuxostat was a novel nonpurine selective inhibitor of xanthine oxidase and a potential alternative to allopurinol. At a daily dose of 80 mg or 120 mg, Febuxostat was more effective than allopurinol at the commonly used fixed daily dose (300 mg) in lowering serum urate, while similar reductions in gout flares and tophus area occurred in all treatment groups (20).

The article which closes our list of top 10 discoveries related to uric acid in the past decade was published by Mazzali et al in *Hypertension* in 2001. The authors tested the hypothesis that uric acid may have a causal role in the development of hypertension and renal disease by examining the effects of mild hyperuricemia in rats, which was induced by providing a uricase inhibitor (oxonic acid) in the diet. Hyperuricemic rats developed elevated blood pressure after 3 weeks, whereas control rats remained normotensive. The development of hypertension was prevented by concurrent treatment with either a xanthine oxidase inhibitor (allopurinol) or a uricosuric agent (benziodarone), both of which lowered uric acid levels. A direct relationship was found between blood pressure and uric acid with blood pressure increase for each 0.03-mmol/L (0.5-mg/dL) incremental rise in serum uric acid. The rats also showed signs of ischemic type of injury of the kidneys with collagen deposition, macrophage infiltration, and an increase in tubular expression of osteopontin, while both the renal injury and hypertension were reduced by treatment with enalapril or L-arginine. The authors concluded that mild hy-

peruricemia caused hypertension and renal injury in the rat via a crystal-independent mechanism, with stimulation of the renin-angiotensin system and inhibition of neuronal NO-synthase (21).

In conclusion, it is clear that the past decade has brought a number of very important new insights about the regulation of uric acid metabolism and the mechanisms that could potentially explain its role in conditions such as gout, infectious diseases, inflammation, hypertension, cardiovascular disease, and renal disease. Still, many more questions have remained unanswered and it will take more time and effort to respond to some of the most fundamental questions posed in the introduction of this article. In the decade to come, we expect that genome-wide association studies will discover many genetic loci that underlie variation in uric acid and predict hyperuricemia, gout, and urolithiasis in humans and experimental animals. Further functional genomics follow-up should explain more general role of caspase-1-activating NALP3 inflammasome and strengthen the evidence for the role of uric acid in innate immunity. The link of uric acid levels with hundreds of so-called "metabolomics" traits will strengthen the evidence for or against the causal role of hyperuricaemia in cardiovascular and metabolic disorders.

The *Croatian Medical Journal* starts 2010 with a theme issue on the topic of uric acid, presenting the efforts of Croatian researchers who have been involved in some of the most significant discoveries achieved over the past several years using the biobank resource "10,001 Dalmatians" (17,22-27). In this issue, Gunjača and colleagues investigate for the first time the value of combining the 8 recently described genetic loci influencing serum uric acid concentration in prediction of hyperuricemia (28). Jerončić and colleagues reported on interactions between genetic variants in SLC2A9 and dietary habits in serum uric acid regulation (29). Polašek and colleagues found for the first time that SLC2A9 was a urate transporter associated not only with gout, but also with nephrolithiasis (30). Polašek and colleagues also found that common variants in SLC17A3 gene affected intra-personal variation in serum uric acid levels in longitudinal time series (31). Finally, Mladen Boban and Darko Modun reviewed the knowledge on the effects of red wine consumption on oxidative stress through temporary postprandial changes in uric acid levels (32). We hope that the decade ahead will bring further progress and at least several unexpected insights that will answer some of the questions related to the role of uric acid in human organism.

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